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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MONTANARI, DAVID A	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 09/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/733,674	JOHNSON ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-36* is/are pending in the application.

4a) Of the above claim(s) *2-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. During a telephone conversation with Greg Giotta, PhD on 8/19/2005 a provisional election was made without traverse to prosecute the invention of Group III, claims 1, and 28-36. Affirmation of this election must be made by applicant in replying to this Office action. Claims 2-27 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-15, 17-20, and 27, drawn to a viral vector encoding a heterologous gene, classified in class 536, subclass 23.1.

II. Claims 16, and 21-26 drawn to a method of killing cancer cells using a viral vector encoding a heterologous gene, classified in class 514, subclass 44.

III. Claims 1, and 28-36, drawn to a viral vector encoding a heterologous gene and further comprising more than one viral packaging sequence, and a method of killing tumor cells using said vector, classified in class 536, subclass 23.1.

Groups I and II are distinct. Group I is drawn to a viral vector encoding a heterologous gene. Group II is drawn to a method of killing cancer cells using a viral vector encoding a heterologous gene. The method of killing cancer cells does not require the vector of group I. Further the vector of group I can be used in other methods other than killing cancer cells.

Groups I and III are distinct. Group I is drawn to a viral vector encoding a heterologous gene. Group III is drawn to a viral vector encoding a heterologous gene and

further comprising more than one viral packaging sequence, and a method of killing tumor cells using said vector. The vector of group I is materially distinct form the vector of group III. Further the vector of group I is not required by the method of group III.

Groups II and III are distinct. Group II is drawn to a method of killing cancer cells using a viral vector encoding a heterologous gene. Group III is drawn to a viral vector encoding a heterologous gene and further comprising more than one viral packaging sequence, and a method of killing tumor cells. The method of killing cancer cell of group II requires materially distinct and separate protocols from the method of killing tumor cells of group III.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper. The examiner would be required to search distinct areas of art for the implementation of the claimed methods and vectors.

2. Claims 1, and 28-36 are examined in the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 1 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 1 of copending Application No. 10/303,598. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim 1 is provisionally rejected under the judicially created doctrine of double patenting over claim 1 of copending Application No. 09/714,409. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: Claim 1 of the instant application encompasses the scope of claim 1 in pending application 09/714,409.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, and 28-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an adenovirus vector comprising the E2F responsive promoter operably linked to an adenovirus immediate early gene and further comprising viral packaging repeat sequences and a method of killing tumor cells using said adenovirus vector *in vitro*, does not reasonably provide enablement for all other virus vectors comprising an E2F responsive promoter operably linked to any viral gene, and a method of killing tumor cells *in vivo* using said virus vector. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice and use the invention commensurate in scope with these claims.

Claims 1, and 28-36 are drawn to a viral vector comprising an E2F responsive transcriptional nucleotide regulatory site that controls the expression of a viral gene, said vector further comprising more than one viral packaging sequence, and a method for killing tumor cells, comprising contacting said tumor cells with said viral vector further comprising more than one viral packaging sequences.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the

claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompass any viral vector comprising an E2F promoter regulating any viral gene and further comprising more than one viral packaging sequences and a method of killing tumor cells *in vivo* using said vector. This embodiment reads on gene therapy.

Whereas the nature of the invention is a method of gene therapy to kill tumor cells using a unique adenoviral vector that targets tumor cells exclusively, the art teaches that such a method would be unpredictable. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three reviews. Concalves (2005, BioEssays, Vol. 27, pgs. 506-517) teaches that with respect to gene therapy "one can conclude that further improvements in gene transfer technologies (e.g. control over transgene expression and integration) and deeper insights in host-vector interactions (e.g. knowledge on vector and gene-modified cell biodistribution following different routes of administration and the impact of innate and adaptive immunity) are warranted before clinical gene therapy reaches maturity" (pg. 514 col. 2 parag. 3). Specifically, Concalves

teaches that gene therapy utilizing viruses has resulted in significant unpredictability, with retroviruses (pg. 513 col. 1 parag. 3 bridge col. 2 parag. 1), and adenoviruses (pg. 513, col. 2 parag. 2) providing only a fleeting success that was ultimately undone by a lack of transduction and low transgene expression levels. Parekh-Olmedo et al. teach (2005, Gene Therapy, Vol. 12, pgs. 639-646) with regard to gene repair utilizing gene therapy comprising single-stranded DNA oligonucleotides, repair of a gene of interest is again unpredictable. Specifically, successful gene repair has been reported in an animal model of severe kidney disease comprising carbonic anhydrase-deficiency utilizing a single-stranded DNA vector (pg. 641 col. 1 parag. 3). However, in a LacZ mouse model designed for testing gene repair using a variety of vectors, no correction of the mutant LacZ gene was observed, resulting in the observation that delivery of DNA to a particular tissue continues to be a problem (pg. 641 col. 2 parag. 1). Verma et al. (2005, Annu. Rev. Biochem. Vol. 74, pgs. 711-738) teach that "the young field of gene therapy promises major medical progress toward a cure of a broad spectrum of human diseases from immunological disorders to heart disease and cancer. It has, therefore, generated great hopes and great hypes, but it has yet to deliver its promised potential" (pg. 732, parag, 2 lines 2-6). Verma et al. continues to teach that the process of gene delivery and expression is known as transduction, and that successful transduction requires overcoming a number of obstacles that are common to all vector systems (pg. 712, parag. 2 lines 1-3). Specifically, these obstacles include production of the vector, the targeting of the vector to a specified cell type, sustained gene expression, and avoidance of potential hazards such as insertional mutagenesis and immune responses (pg. 712, parag. 2 lines 3-19).

In view of the unpredictability of the art of gene therapy, a skilled artisan would require specific guidance in the instant disclosure to make and use the full scope of the claimed embodiment. Wherein the instant specification provides specific guidelines for targeting an isolated tumor cell *in vitro*, the instant specification however, has not provided any relevant teachings, guidance, or working examples that teach or otherwise correlate to targeting tumor cells *in vivo* with one of the claimed viral vectors that would lead to the death of said tumor cells. The specification has failed to provide any guidance or working examples that correlate administration of said expression vectors into a host with targeting of a particular cell or tissue. One of normal skill in the art would not be able to rely on the state of the art of *in vivo* gene therapy to target and kill tumor cells using the claimed viral vector(s). Thus in view of the lack of guidance and direction provided by the specification for gene therapy of tumor cells in any animal, it would have required one of skill in the art undue experimentation to make and use the invention as claimed.

With regard to the claimed vector it is apparent from the instant specification and the prior art cited in pgs. 3-6 of the instant specification that in order to make and use the claimed invention when read within the context of the as-filed specification, an E2F responsive promoter must be operably linked to an adenovirus immediate early gene so as to render the replication of the modified adenovirus vector conditional, thereby exhibiting applicant's application of the vector for selectively killing neoplastic cells with little or no killing on non-neoplastic cells (pg. 6 of the specification). It is not apparent how a skilled artisan makes and uses an adenovirus vector comprising an E2F responsive promoter operably linked to any other adenovirus gene so as to achieve applicant's intended application of a tissue specific and replication competent

adenovirus vector. Moreover, it is well-established in the numerous cited prior art from the as-filed specification, that a sufficient amount of an adenovirus early gene intended targeted for its controllable transcriptional activity must be generated in order to replicate the modified adenovirus vectors inside transfected neoplastic cells. Within this context, the instant specification and the prior art provided by the instant specification only provides sufficient guidance for achieving this controllable transcriptional activity by teaching the operable linkage of an E2F responsive promoter to an adenoviral immediate early gene in an adenovirus vector. As such, it is apparent on the basis of the instant specification and the prior art provided by the instant specification that only the subject matter drawn to a replication competent adenovirus vector comprising an E2F responsive promoter operably linked to an adenovirus immediate early gene is reasonably enabling at the time the invention was made.

The working examples provided by the specification teach the construction of the adenoviral E2F-1E4 vector (pg. 30 bridge pg. 31 lines 1-18), the E2F1-E4 vector (pg. 31 lines 20-32 bridge pg. 32 lines 1-3) the EDF1-E1a vector (pg. 32 lines 26-32 bridge pg. 34 lines 1-14), the E2F1-E1a/E2F1-E4 vector (pg. 32 lines 26-32 bridge pg. 34 lines 1-14), and the Onxy-443 (pg. 36 lines 5-30 bridge pg. 37 lines 1-11). The specification continues to teach A549 (lung carcinoma) cells were transfected *in vitro* with 3 different viral vectors ONYX-451, ONYX-452, and ONYX-455 (pg. 42 lines 10-19). The specification continues to teach that adenoviral vectors comprising the E2F-1 promoter preferentially target cancerous cells compared to non-cancerous cells *in vitro* (pg. 7 lines 15-19). Though the art of record (Parr) does teach *in vivo* targeting and expression of the beta-galactosidase gene and the herpes thymidine kinase gene using a vector comprising the E2F-1 promoter, the art of record does not teach the killing of tumor cells *in vivo*

using said vector. Thus the specification has failed to teach *in vivo* killing of any tumor cells using the claimed vectors. The specification has only disclosed using the claimed vectors for *in vitro* targeting of cancerous cells compared to non-cancerous cells. In view of the art of record discussed above regarding the unpredictability of gene therapy the skilled artisan would not be enabled for the full breadth of the claimed invention.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its full breadth and limiting the scope of the claimed invention to an adenovirus vector comprising the E2F responsive promoter operably linked to an adenovirus immediate early gene and further comprising viral packing repeats and a method of killing tumor cells *in vitro* is proper.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Parr et al. (1997, Nature Medicine, Vol. 3, pgs. 1145-1149).

Claims 1 and 28-29 are drawn to a viral vector comprising an E2F responsive transcriptional nucleotide regulatory site that controls the expression of a viral gene.

Parr et al. teach a viral vector comprising the E2F1 promoter that controls the herpes thymidine kinase gene (pg. 1147, col.1, parag. 1 lines 1-5). Parr continues to teach that said vector was made using the Ad.5 backbone (pg. 1145, Fig. 1). In view of the following reference (Schmid) that viral packaging sequences are inherent in the Ad.5 genome, they would thus be in the vector taught by Parr. Therefore Parr et al. clearly anticipate the invention of claims 1 and 28-29.

Claim 34-35 are rejected under 35 U.S.C. 102(b) as being anticipated by Schmid et al. (1997, J. of Virology, Vol. 71, pgs. 3375-3384).

Claims 34-35 are drawn to a viral vector comprising more than one packaging sequence, wherein said viral vector is an adenoviral vector.

Schmid et al. teach adenoviral vectors (Ad.5) comprising the AI through AVII viral packaging sequences (pg. 3377 col. 2 parag. 1 and fig. 2). Therefore Schmid et al. clearly anticipate the inventions of claims 34-35.

Claims 30-33, and 36 are free of the prior art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is 1-571-272-3108. The examiner can normally be reached on M-F 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 1-571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Montanari, PhD

RAM R. SHUKLA, PH.D.
SUPERVISORY PATENT EXAMINER